Optimal timing of anticoagulation after acute ischaemic stroke with atrial fibrillation (OPTIMAS): a multicentre, blinded-endpoint, phase 4, randomised controlled trial

*David J Werring, Hakim-Moulay Dehbi, Norin Ahmed, Liz Arram, Jonathan G Best, Maryam Balogun, Kate Bennett, Ekaterina Bordea, Emilia Caverly, Marisa Chau, Hannah Cohen, Mairead Cullen, Caroline J Doré, Stefan T Engelter, Robert Fenner, Gary A Ford, Aneet Gill, Rachael Hunter, Martin James, Archana Jayanthi, Gregory Y H Lip, Sue Massingham, Macey L Murray, Iwona Mazurczak, Philip S Nash, Amalia Ndoutoumou, Bo Norrving, Hannah Sims, Nikola Sprigg, Tishok Vanniyasingam, Nick Freemantle, on behalf of the OPTIMAS investigators**

Summary

Background The optimal timing of anticoagulation for patients with acute ischaemic stoke with atrial fibrillation is uncertain. We investigated the efficacy and safety of early compared with delayed initiation of direct oral anticoagulants (DOACs) in patients with acute ischaemic stroke associated with atrial fibrillation.

Methods We performed a multicentre, open-label, blinded-endpoint, parallel-group, phase 4, randomised controlled trial at 100 UK hospitals. Adults with atrial fibrillation and a clinical diagnosis of acute ischaemic stroke and whose physician was uncertain of the optimal timing for DOAC initiation were eligible for inclusion in the study. We randomly assigned participants (1:1) to early (ie, ≤4 days from stroke symptom onset) or delayed (ie, 7–14 days) anticoagulation initiation with any DOAC, using an independent online randomisation service with random permuted blocks and varying block length, stratified by stroke severity at randomisation. Participants and treating clinicians were not masked to treatment assignment, but all outcomes were adjudicated by a masked independent external adjudication committee using all available clinical records, brain imaging reports, and source images. The primary outcome was a composite of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassifiable stroke, or systemic embolism incidence at 90 days in a modified intention-to-treat population. We used a gatekeeper approach by sequentially testing for a non-inferiority margin of 2 percentage points, followed by testing for superiority. OPTIMAS is registered with ISRCTN (ISRCTN17896007) and ClinicalTrials.gov (NCT03759938), and the trial is ongoing.

Findings Between July 5, 2019, and Jan 31, 2024, 3648 patients were randomly assigned to early or delayed DOAC initiation. 27 participants did not fulfil the eligibility criteria or withdrew consent to include their data, leaving 3621 patients (1814 in the early group and 1807 in the delayed group; 1981 men and 1640 women) in the modified intention-to-treat analysis. The primary outcome occurred in 59 (3·3%) of 1814 participants in the early DOAC initiation group compared with 59 (3·3%) of 1807 participants in the delayed DOAC initiation group (adjusted risk difference [RD] 0·000, 95% CI –0·011 to 0·012). The upper limit of the 95% CI for the adjusted RD was less than the non-inferiority margin of 2 percentage points ($p_{non\text{-}inferiority}$=0·0003). Superiority was not identified ($p_{superiority}$=0·96). Symptomatic intracranial haemorrhage occurred in 11 (0·6%) participants allocated to the early DOAC initiation group compared with 12 (0·7%) participants allocated to the delayed DOAC initiation group (adjusted RD 0·001, –0·004 to 0·006; p=0·78).

Interpretation Early DOAC initiation within 4 days after ischaemic stroke associated with atrial fibrillation was non-inferior to delayed initiation for the composite outcome of ischaemic stroke, intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days. Our findings do not support the current common and guideline-supported practice of delaying DOAC initiation after ischaemic stroke with atrial fibrillation.

Funding British Heart Foundation.

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Published Online
October 24, 2024
https://doi.org/10.1016/S0140-6736(24)02197-4

See Online/Comment
https://doi.org/10.1016/S0140-6736(24)02259-1

*Investigators at recruiting sites that recruited participants are listed in the appendix

Stroke Research Centre, Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology, London, UK (Prof D J Werring PhD FRCP, L Arram MSc, J G Best PhD, S Massingham RGN, P S Nash MSci); **Comprehensive Stroke Service, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK** (Prof D J Werring); **Comprehensive Clinical Trials Unit at UCL** (H-M Dehbi PhD, N Ahmed MSc, M Balogun MSc, K Bennett MSc, E Bordea PhD, E Caverly MSc, M Chau BBNS(Hons), M Cullen MSc, Prof C J Doré BSc, R Fenner MA, A Gill MSc, Prof R Hunter PhD, A Jayanthi MSc, I Mazurczak PhD, A Ndoutoumou MPharm, H Sims MSc, T Vanniyasingam MSc, Prof N Freemantle PhD) **and MRC Clinical Trials Unit** (M L Murray PhD), **Institute of Clinical Trials and Methodology, University College London, London, UK; Research Department of Haematology, University College London, London, UK** (H Cohen MD); **Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK** (H Cohen); **Neurology and Neurorehabilitation, University Department of Geriatric**

Introduction

Atrial fibrillation is present in at least 20% of all patients with ischaemic stroke and is likely to be the cause of the event in these patients.[1] Large randomised trials of direct oral anticoagulants (DOACs) have confirmed that long-term oral anticoagulation reduces the risk of ischaemic stroke in people with atrial fibrillation by around two-thirds,[2,3] with a low risk of intracranial haemorrhage. However, because these trials excluded patients with acute ischaemic stroke (within 7–30 days before eligibility assessment), the optimal timing of anticoagulation soon after acute ischaemic stroke is uncertain. Clinicians

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Medicine Felix Platter, University of Basel, Basel, Switzerland (Prof S T Engelter MD)**; Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (Prof G A Ford MD)**; Medical Sciences Division, University of Oxford, Oxford, UK** (Prof G A Ford)**; Royal Devon and Exeter Hospital, Exeter, UK** (Prof M James MD FRCP)**; University of Exeter Medical School, Exeter, UK** (Prof M James)**; Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK** (Prof G Y H Lip MD)**; Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark** (Prof G Y H Lip)**; Department of Clinical Sciences and Department of Neurology, Skåne University Hospital, Lund University, Lund, Sweden** (Prof B Norrving MD)**; Stroke Trials Unit, Division of Mental Health and Clinical Neuroscience, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK** (Prof N Sprigg FRCP)

Correspondence to:
Prof David J Werring, Stroke Research Centre, Department of Brain Repair and Rehabilitation, University College London Queen Square Institute of Neurology, London WC1B 5EH, UK
d.werring@ucl.ac.uk

See Online for appendix

Research in context

Evidence before this study

We searched the electronic databases PubMed, Embase, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published in English from inception to May 16, 2024, comparing different timings of direct oral anticoagulant (DOAC) initiation for adult patients (aged ≥18 years) with a clinical diagnosis of acute ischaemic stroke and atrial fibrillation. We identified two published studies (TIMING and ELAN) and one study published in abstract form (START). TIMING, an open-label, non-inferiority trial, which randomly assigned participants to early (ie, ≤4 days after stroke onset) or delayed (ie, 5–10 days after stroke onset) DOAC initiation, recruited 888 of 3000 planned participants. The primary outcome, a composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality at 90 days, occurred in 31 (6·89%) of 450 patients assigned to early initiation and in 38 (8·68%) of 438 patients assigned to delayed direct oral anticoagulant initiation (absolute risk difference −1·79%, 95% CI −5·31 to 1·74; $p_{non\text{-}inferiority}$=0·004). The risk of ischaemic stroke was 3·11% in patients who started anticoagulation early, compared with 4·57% in patients who started later, with no intracerebral haemorrhages. In the ELAN trial, in which participants were randomly assigned to early (ie, ≤48 h after stroke onset in participants with minor or moderate stroke or on day 6 or 7 in those with major stroke) or later DOAC initiation (ie, on day 3 or 4 in participants with minor stroke, day 6 or 7 in those with moderate stroke, or day 12, 13, or 14 in those with major stroke), the primary outcome (ie, a composite of symptomatic intracranial haemorrhage, major extracranial bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death within 30 days) occurred in 29 (2·9%) of 1006 participants in the early treatment group and 41 (4·1%) of 1007 participants in the delayed treatment group (risk difference −1·18 percentage points, 95% CI −2·84 to 0·47). Recurrent ischaemic stroke occurred in 14 (1·4%) participants in the early treatment group and 25 (2·5%) participants in the delayed treatment group (odds ratio 0·57, 95% CI 0·29 to 1·07), and symptomatic intracranial haemorrhage occurred in four participants in the study (two in each treatment group [0·2%]).

Added value of this study

OPTIMAS is the largest trial of DOAC initiation timing in patients with acute ischaemic stroke with atrial fibrillation, providing more precise estimates than previous trials of early DOAC initiation on recurrent ischaemic stroke and the risk of intracranial haemorrhage in a broad patient population. We included many people with moderate-to-severe stroke (528 [14·6%] of 3621 participants with a National Institutes of Health Stroke Scale score of >10 at randomisation), in whom there is greater concern about intracranial haemorrhage than for people with less severe stroke. Our findings provide reassurance that early DOAC initiation is non-inferior to delayed DOAC initiation for a composite outcome of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassified stroke, or systemic embolism. We identified no evidence for heterogeneity of the effect of anticoagulation timing in participants with moderate-to-severe stroke, patients who received acute reperfusion treatments (ie, intravenous thrombolysis, mechanical thrombectomy, or both), or those who were already taking an anticoagulant, providing reassurance that early DOAC initiation does not carry a high risk of symptomatic intracranial haemorrhage in these patient groups.

Implications of all the available evidence

The available evidence indicates that early DOAC initiation is non-inferior to delayed initiation after ischaemic stroke with atrial fibrillation and does not support the common and guideline-recommended practice of delaying treatment due to concerns about intracranial haemorrhage, irrespective of baseline stroke severity. A planned individual participant data meta-analysis will provide additional information on the benefits and risks of early DOAC initiation following acute ischaemic stroke associated with atrial fibrillation.

should balance the risks of ischaemic stroke recurrence and intracranial haemorrhage, both of which are most likely to occur in the first few days after acute ischaemic stroke associated with atrial fibrillation. Early anticoagulation might prevent recurrent ischaemic strokes but could increase the risk of intracranial haemorrhage, including intracerebral haemorrhage due to haemorrhagic transformation of the acute infarct. Haemorrhagic transformation is most common within large infarcts (eg, affecting the full territory of the middle, posterior, or anterior cerebral arteries) and can be associated with an increased risk of death or disability if it is accompanied by acute neurological deterioration.[4]

In the absence of high-quality evidence, guidelines on when to start oral anticoagulation are varied and inconsistent; whereas some clinicians advocate the 1-3-6-12-day rule to guide the timing of anticoagulation initiation after stroke based on clinical stroke severity (ie, 1 day for transient ischaemic attack, 3 days for mild stroke [National Institutes of Health Stroke Scale (NIHSS) score <8], 6 days for moderate stroke [NIHSS score 8–15], or 12 days for severe stroke [NIHSS score ≥16]),[5] others recommend delaying anticoagulation for 2 weeks in patients with severe stroke syndromes or large infarcts.[6] The absence of high-quality evidence has led to uncertainty among physicians and recommendations for randomised interventional trials.[7–9]

Randomised and observational evidence suggested that early anticoagulation might reduce the risk of ischaemic stroke without an increase in intracranial haemorrhage[10,11] and provided estimates of event rates[12] but did not conclusively show whether early anticoagulation is safe

or superior to delayed treatment. Other limitations of the available data are the inclusion of few participants with moderate-to-severe stroke, with haemorrhagic transformation of the acute infarct, or who are already taking oral anticoagulants.

The Optimal Timing of Anticoagulation After Acute Ischaemic Stroke (OPTIMAS) trial aimed to establish the safety and efficacy of early anticoagulation with a DOAC in a broad population of people with acute ischaemic stroke associated with atrial fibrillation.

Methods

Study design and participants

OPTIMAS is a phase 4, multicentre, parallel-group, randomised controlled trial with an open-label intervention, blinded endpoint adjudication, and a hierarchical non-inferiority–superiority gatekeeper design, comparing a policy of early DOAC initiation (ie, within 4 days of stroke onset) with delayed initiation (ie, 7–14 days from stroke onset) in patients with atrial fibrillation and acute ischaemic stroke. The trial was conducted at 100 hospitals within the UK (appendix pp 4–7).

Participants were recruited at hospital stroke units by appropriately trained local research team investigators. Adult patients (ie, aged ≥18 years) were eligible for inclusion if they had atrial fibrillation confirmed by an electrocardiogram or medical records; had a clinical diagnosis of acute ischaemic stroke with symptoms lasting more than 24 h and at least one form of brain imaging (ie, CT or MRI) to exclude intracranial haemorrhage and non-stroke diagnoses, with recommendations to undertake MRI to define lesion location and anatomy, and repeat imaging (with CT or MRI) to assess for haemorrhagic transformation before anticoagulation; and were eligible for anticoagulation with a DOAC with the responsible treating physician uncertain of the optimal timing to start anticoagulation. Patients were not eligible if they had a coagulopathy, evidence of recent or current anticoagulation with a vitamin K antagonist leading to an international normalised ratio of 1·7 or higher at randomisation; had clinically significant thrombocytopenia (ie, platelet count $<75\times10^9$ platelets per L); had other coagulopathy or bleeding tendency judged to contraindicate anticoagulation by the treating clinician; had severe haemorrhagic transformation of the acute infarct (ie, parenchymal haematoma type 2 according to the Heidelberg criteria)[13] or acute intracranial haemorrhage unrelated to the acute infarct; had a contraindication to DOAC use (eg, severe renal impairment [creatinine clearance <15 mL/min], cirrhosis [with Child Pugh classification B or C], alanine aminotransferase more than 2-times the upper limit of normal, or concurrent medication with a notable DOAC interaction [eg, strong CYP3A4 inducers]); had a known allergy or intolerance to Factor Xa and direct thrombin inhibitor; had a definite indication for use of a vitamin K antagonist (eg, a mechanical heart valve); were pregnant or breastfeeding; had brain imaging evidence of non-stroke pathology judged likely to explain clinical presentation (eg, mass lesion or encephalitis); could not be followed up for 90 days after trial entry; did not agree to provide consent to study procedures, including the site informing general practitioner and health-care professional responsible for anticoagulation care of participants; had any other contraindication to early anticoagulation as judged by the treating clinician; or had any other reason that the treating clinician considered would make the patient unsuitable to enter OPTIMAS.

All participants (or an appropriate consultee according to relevant national regulations) provided written informed consent. The trial was approved by the National Health Service Health Research Authority (South Central [Oxford B] Research Ethics Committee; reference number 19/SC/0021). The trial protocol is shown in the appendix (pp 17–97). OPTIMAS was prospectively registered with the International Standard Randomised Controlled Trial Number Registry (ISRCTN17896007) and ClinicalTrials.gov (NCT03759938), and the trial is ongoing.

Randomisation and masking

Participants were enrolled and randomly assigned by appropriately trained local research team investigators in a 1:1 ratio to early DOAC initiation (ie, within 4 days of stroke onset or the time that symptoms were first noted if the onset time could not be determined) or delayed DOAC initiation (ie, 7–14 days after onset, an interval selected based on a 2018 survey of UK practice[7]) using an independent online randomisation service with random permuted blocks and randomly varying block lengths, stratified by NIHSS score at randomisation (ie, 0–4, 5–10, 11–15, 16–21, or >21), but not by study site, which could be a source of allocation bias if included. The participant and treating clinicians were not masked to allocation, but all outcomes were adjudicated by a masked independent external adjudication committee (appendix p 3).

Procedures

The trial methods have previously been published in detail.[14] At enrolment, we collected detailed clinical information about baseline vascular risk factors and medical history via case report forms, including documentation of atrial fibrillation; blood pressure; weight; concomitant medication; NIHSS score at admission and randomisation; estimated pre-stroke modified Rankin Scale (mRS) score; cognition (measured with the Informant Questionnaire on Cognitive Decline in the Elderly); quality of life (measured with EQ-5D-5L); and blood tests, including for creatinine, alanine aminotransferase, platelet count, and international normalised ratio. Sex and ethnicity data were collected by research practitioners at study sites. After randomisation the responsible treating clinician decided the exact timing of anticoagulation within the

assigned timeframe for early or delayed DOAC initiation. Antiplatelet agents were permitted (before DOAC initiation) after the stroke in line with current practice at the discretion of the treating physician. Any DOAC licensed for stroke prevention in atrial fibrillation (ie, apixaban, dabigatran, edoxaban, or rivaroxaban) was permitted, with the dose and route of administration (usually swallowed as tablets) decided by the physician responsible for the participant; criteria for dose reduction and methods of administration are provided in the relevant summary of product characteristics for each DOAC.[15–18] We recorded data on the timing and dose of a DOAC received by all participants and whether these doses were within the allocated early or late time window and in line with guideline-based dose reduction criteria.[19] However, because OPTIMAS was a phase 4 trial testing a policy of early versus delayed DOAC initiation within a licensed indication, we did not consider doses that were higher or lower than recommended in guidelines to be protocol deviations. All other stroke care followed current UK best practice. We assessed response and need for altered treatment and serious adverse events throughout the treatment period, at discharge, and during follow-up.

All brain and angiographic imaging (ie, CT, MRI, CT angiography, and magnetic resonance angiography) data obtained as part of clinical care were requested and collected as anonymised Digital Imaging and Communication in Medicine (DICOM) images for standardised central analysis.

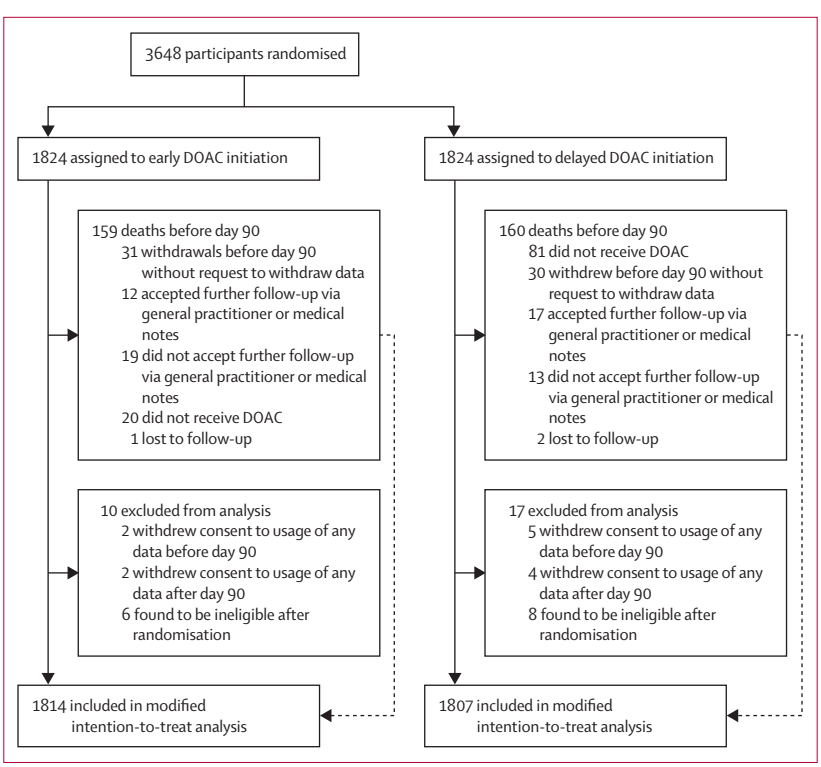
3648 participants randomised
1824 assigned to early DOAC initiation
1824 assigned to delayed DOAC initiation
159 deaths before day 90
31 withdrawals before day 90 without request to withdraw data
12 accepted further follow-up via general practitioner or medical notes
19 did not accept further follow-up via general practitioner or medical notes
20 did not receive DOAC
1 lost to follow-up
160 deaths before day 90
81 did not receive DOAC
30 withdrew before day 90 without request to withdraw data
17 accepted further follow-up via general practitioner or medical notes
13 did not accept further follow-up via general practitioner or medical notes
2 lost to follow-up
10 excluded from analysis
2 withdrew consent to usage of any data before day 90
2 withdrew consent to usage of any data after day 90
6 found to be ineligible after randomisation
17 excluded from analysis
5 withdrew consent to usage of any data before day 90
4 withdrew consent to usage of any data after day 90
8 found to be ineligible after randomisation
1814 included in modified intention-to-treat analysis
1807 included in modified intention-to-treat analysis

Figure 1: **Trial profile**
DOAC=direct oral anticoagulant.

Follow-up data on primary and secondary outcomes at 90 days were collected with standardised case report forms at face-to-face visits by appropriately trained local research team investigators. We collected data on mRS score, quality of life (measured with the EQ-5D-5L), concomitant medication, cognition (measured with the Montreal Cognitive Assessment), patient-reported outcomes (measured with the Patient-reported Outcomes Measurement Information System-10), and health and social care resources usage (measured with a study-specific questionnaire). If a face-to-face visit was not possible then follow-up by telephone or postal questionnaire was permitted. In exceptional circumstances (eg, staffing challenges during the COVID-19 pandemic) the central study site (University College London [UCL] Stroke Research Centre) conducted the 90-day follow-up on the individual site's behalf.

Trial data were collected via a secure online electronic data capture system, and pseudonymised clinical imaging data were collected via a secure file transfer portal. Data management and monitoring were done by the Comprehensive Clinical Trials Unit at UCL.

Outcomes

The primary outcome was a composite of recurrent ischaemic stroke, symptomatic intracranial haemorrhage (including haemorrhagic transformation of the qualifying acute infarct), unclassifiable stroke syndromes (ie, patients in whom a clinical diagnosis of a stroke syndrome was made but who did not undergo neuroimaging for clinical reasons, such as a terminal prognosis), and systemic arterial embolism incidence within 90 days after randomisation in a modified intention-to-treat population, and was measured with data entered by trained local investigators using standardised case report forms. All reported outcome event data were assessed by a masked internal validation committee. All primary outcome events were adjudicated centrally by an independent external adjudication committee of expert clinicians (appendix p 3) who were masked to treatment allocation, using all available information, including site case report forms, clinical reports, and anonymised DICOM brain images.

Secondary outcomes were also measured in the modified intention-to-treat population. Secondary efficacy outcomes were the incidence of the individual components of primary outcome within 90 days; all-cause and cardiovascular mortality within 90 days; incidence of venous thromboembolism within 90 days; functional status (mRS score[20]) at 90 days; cognitive ability (Montreal Cognitive Assessment score) at 90 days; quality of life (EQ-5D-5L score) at 90 days; patient-reported outcomes (Patient-reported Outcomes Measurement Information System score) at 90 days; rate of taking the assigned anticoagulation treatment at 90 days; time to first incidence of the primary outcome;

time to first incidence for overall survival (all-cause mortality); time to first incidence of the primary outcome or overall survival (all-cause mortality); time to first incidence of a composite of ischaemic stroke or systemic embolism; time to first incidence of symptomatic intracranial haemorrhage; time to first incidence of recurrent ischaemic stroke; time to first incidence of systemic arterial embolism; length of hospital stay; and health and social care resource use (measured with a study-specific questionnaire). We did not collect centrally adjudicated data on cardiovascular mortality, so this outcome is not reported. Analyses of cognitive, functional, quality-of-life, and health economic data (including length of hospital stay) are ongoing and will be reported elsewhere. Safety outcomes were symptomatic intracranial haemorrhage, its anatomical subtypes (ie, extradural, subdural, subarachnoid, intracerebral, and intraventricular), major extracranial bleeding,[21] clinically relevant non-major extracranial bleeding, and all major bleeding within 90 days.[22]

Prespecified secondary analyses included subgroup analyses by stroke severity, reperfusion treatment (ie, with intravenous thrombolysis, mechanical thrombectomy, or both), and previous anticoagulation. In addition to analysing time to first incidence of the composite primary outcome plus overall survival, we also performed a post-hoc analysis of the incidence of this composite outcome in the modified intention-to-treat population to further explore the effect of the competing risk of death on our primary outcome. Brain imaging analyses will be reported separately.

When a suspected adverse event occurred, the principal investigator or delegate at each site assessed for seriousness; all serious adverse events were recorded and reported to the central study team.

Statistical analysis

The statistical analysis plan was finalised and approved on July 3, 2024, by the trial steering committee, before database lock on July 25, 2024, and is shown in the appendix (pp 97–133).

Our initial power calculation assumed a reduction in the primary outcome event rate from 11·5% in the delayed DOAC initiation group to 8% in the early DOAC initiation group (a relative risk reduction of 30%) based on the Virtual International Stroke Trials Archive of trials in patients with ischaemic stroke and atrial fibrillation, giving a planned sample size of 3478 patients.[23] The sample size calculation used 90% power for superiority, a two-sided significance level of 5%, and was inflated by 10% for loss to follow-up. Based on the expected event rate and a non-inferiority margin of 3%, a sample size of 3478 evaluable participants would have 80% power for non-inferiority.[14] We re-evaluated study power in November, 2021, at the request of the independent data monitoring committee

	Early initiation (n=1814)	Delayed initiation (n=1807)	Total (n=3621)
Age, years	78·5 (9·9)	78·5 (9·9)	78·5 (9·9)
Sex			
Female	810 (44·7%)	830 (45·9%)	1640 (45·3%)
Male	1004 (55·3%)	977 (54·1%)	1981 (54·7%)
Ethnicity			
White	1690 (93·2%)	1703 (94·2%)	3393 (93·7%)
Black, Black British, Caribbean, or African	31 (1·7%)	27 (1·5%)	58 (1·6%)
South Asian	30 (1·7%)	30 (1·7%)	60 (1·7%)
East Asian or southeast Asian	23 (1·3%)	17 (0·9%)	40 (1·1%)
Mixed ethnicity, other, not disclosed, or missing	40 (2·2%)	30 (1·7%)	70 (1·9%)
Anticoagulant agent taken before ischaemic stroke			
Vitamin K antagonist	61 (3·4%)	53 (2·9%)	114 (3·1%)
DOAC	582 (32·1%)	584 (32·3%)	1166 (32·2%)
Antiplatelet agent taken before ischaemic stroke	213 (11·7%)	194 (10·7%)	407 (11·2%)
Antiplatelet agent taken after ischaemic stroke	1489 (82·1%)	1546 (85·6%)	3035 (83·8%)
DOAC initiated after ischaemic stroke			
Apixaban	1142 (63·0%)	1106 (61·2%)	2248 (62·1%)
Dabigatran	38 (2·1%)	31 (1·7%)	69 (1·9%)
Edoxaban	537 (29·6%)	508 (28·1%)	1045 (28·9%)
Rivaroxaban	78 (4·3%)	87 (4·8%)	165 (4·6%)
Did not commence DOAC	19 (1·0%)	75 (4·2%)	94 (2·6%)
Intravenous thrombolysis treatment	421 (23·2%)	377 (20·9%)	798 (22·0%)
Endovascular treatment	131 (7·2%)	135 (7·5%)	266 (7·3%)
Hypercholesterolaemia	620 (34·2%)	568 (31·4%)	1188 (32·8%)
Diabetes type 1 or 2, known before ischaemic stroke or diagnosed during admission	392 (21·6%)	376 (20·8%)	768 (21·2%)
Hypertension	1205 (66·4%)	1229 (68·0%)	2434 (67·2%)
Chronic kidney disease	271 (14·9%)	272 (15·1%)	543 (15·0%)
Dementia or cognitive impairment	121 (6·7%)	127 (7·0%)	248 (6·8%)
Smoking status			
Current smoker	144 (7·9%)	129 (7·1%)	273 (7·5%)
Ex-smoker	502 (27·7%)	517 (28·6%)	1019 (28·1%)
Never smoked	946 (52·1%)	970 (53·7%)	1916 (52·9%)
Not known	222 (12·2%)	191 (10·6%)	413 (11·4%)
Current alcohol intake >14 units per week	213 (11·7%)	189 (10·5%)	402 (11·1%)
Myocardial infarction	162 (8·9%)	174 (9·6%)	336 (9·3%)
Coronary revascularisation	109 (6·0%)	120 (6·6%)	229 (6·3%)
Congestive heart failure	210 (11·6%)	173 (9·6%)	383 (10·6%)
History of angina	139 (7·7%)	123 (6·8%)	262 (7·2%)
Peripheral arterial disease	30 (1·7%)	48 (2·7%)	78 (2·2%)
Previous ischaemic stroke	295 (16·3%)	242 (13·4%)	537 (14·8%)
Previous intracranial haemorrhage	35 (1·9%)	28 (1·5%)	63 (1·7%)
Atrial fibrillation known before ischaemic stroke	917 (50·6%)	919 (50·9%)	1836 (50·7%)

(Table 1 continues on next page)

	Early initiation (n=1814)	Delayed initiation (n=1807)	Total (n=3621)
(Continued from previous page)			
Type of atrial fibrillation			
Paroxysmal	468 (25·8%)	498 (27·6%)	966 (26·7%)
Persistent	1297 (71·5%)	1264 (70·0%)	2561 (70·7%)
Atrial flutter	48 (2·6%)	44 (2·4%)	92 (2·5%)
Missing	1 (0·1%)	1 (0·1%)	2 (0·1%)
Previous hospitalisation for extracranial haemorrhage	38 (2·1%)	30 (1·7%)	68 (1·9%)
NIHSS score at admission			
0–4	723 (39·9%)	762 (42·2%)	1485 (41·0%)
5–10	616 (34·0%)	612 (33·9%)	1228 (33·9%)
11–15	237 (13·1%)	200 (11·1%)	437 (12·1%)
16–21	165 (9·1%)	152 (8·4%)	317 (8·8%)
>21	65 (3·6%)	72 (4·0%)	137 (3·8%)
Missing	8 (0·4%)	9 (0·5%)	17 (0·5%)
NIHSS score at randomisation			
0–4	1039 (57·3%)	1044 (57·8%)	2083 (57·5%)
5–10	505 (27·8%)	505 (27·9%)	1010 (27·9%)
11–15	147 (8·1%)	135 (7·5%)	282 (7·8%)
16–21	90 (5·0%)	88 (4·9%)	178 (4·9%)
>21	33 (1·8%)	35 (1·9%)	68 (1·9%)
NIHSS score at admission	6 (3–11)	5 (3–10)	5 (3–10)
NIHSS score at randomisation	4 (2–7)	4 (2–7)	4 (2–7)

Data are mean (SD), n (%), and median (IQR). DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale.

Table 1: **Participant characteristics at randomisation, by treatment group**

due to a lower-than-expected interim adjudicated overall primary outcome rate of 4·3% (ie, both groups combined). We also reconsidered the non-inferiority margin, and decided on 2 percentage points, which is consistent with clinically meaningful absolute risk differences observed in secondary stroke prevention trials.[24] We regarded an absolute risk increase in our primary outcome of 2% from an expected baseline event rate of about 4% to be considered clinically important and discouraging for the use of early DOAC initiation. With the lower primary outcome event rate of 4·3%, our planned sample size of 3478 patients had 80% power to show non-inferiority (based on an absolute non-inferiority margin of 2 percentage points, assuming an equal rate of 4·3% in both groups and a two-sided alpha of 5%) and 80% power for superiority assuming an odds ratio of 0·62 with an event rate in the control group of 5·3%. In November, 2023, the trial steering committee and independent data monitoring committee recommended continuation of recruitment for as long as trial funding allowed, ultimately leading to a larger sample size of 3648 participants.

Analyses followed the modified intention-to-treat principle, excluding participants who had been randomly assigned to a treatment group but were ineligible because they did not have both confirmed atrial fibrillation and ischaemic stroke. Primary outcome data were collected from all participants enrolled, but participants who requested complete data erasure were removed from all analyses. We used a gatekeeper design, first testing for non-inferiority of the intervention, using a non-inferiority margin of 2%. After non-inferiority was established, we then tested for superiority. For the primary outcome, we used mixed-effects logistic regression, including an independent variable indicating treatment allocation, with adjustment for stroke severity (based on NIHSS score) at randomisation. Sites were included as random intercept terms. Prespecified secondary analyses included subgroup analyses by stroke severity, reperfusion treatment (ie, with intravenous thrombolysis, mechanical thrombectomy, or both), and previous anticoagulation, which were conducted by fitting an interaction term between the characteristic of interest and DOAC initiation timing. We also plan to do prespecified exploratory analyses to investigate the effects of DOAC initiation according to brain imaging biomarkers, including haemorrhagic transformation (ie, presence and subtypes[13]), infarct volume, and markers of cerebral small vessel disease, which we will report separately when all analyses are completed.

The trial was monitored by an independent data monitoring committee (appendix p 3), which conducted regular 6-monthly reviews of trial safety. Statistical analyses were performed in Stata 18, R (version 4.4.1), and SAS (version 9.14).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 5, 2019, and Jan 31, 2024, 3648 participants were enrolled at 96 of 100 activated sites (figure 1). 1824 participants were randomly assigned to early DOAC initiation (ie, ≤4 days), and 1824 participants were randomly assigned to delayed DOAC initiation (ie, 7–14 days). The mean timing of DOAC initiation (from stroke onset) in the early initiation group was 3·1 days (SD 1·8; 74·3 h [44·2]), compared with 8·3 days (3·1; 200·0 h [74·4]) in the delayed initiation group. The mean time from randomisation to DOAC initiation was 1·0 day (SD 1·8; 24·5 h [44·0]) in the early initiation group and 6·2 days (3·1; 149·6 h [75·0]) in the delayed initiation group. Participant baseline characteristics are shown in table 1. Detailed information on DOAC doses recorded for both groups in relation to UK guideline recommendations[19] is shown in the appendix (p 8). 75 (2·1%) of 3621 participants received a DOAC more than 24 h outside their allocated time window: 20 (0·6%) in the early initiation group and 55 (1·5%) in the delayed initiation group. There were 26 (0·7%) crossovers into the non-allocated time window: 12 (0·3%) in the early initiation group and 14 (0·4%) in the delayed initiation group.

Our modified intention-to-treat population included 1814 individuals in the early DOAC initiation group and 1807 in the delayed DOAC initiation group, as ten participants in the early DOAC initiation group and 17 in the delayed DOAC initiation group did not have a confirmed diagnosis of both acute ischaemic stroke and atrial fibrillation or withdrew from the study and requested complete data erasure (figure 1). Participants' baseline characteristics were well balanced for all major prognostic and potential confounding factors (table 1). The baseline characteristics of the 3621 patients included in the modified intention-to-treat analysis were not systematically different from the 27 patients who were excluded (appendix p 9). 891 (24·6%) of 3621 participants had moderate-to-severe stroke (ie, NIHSS score >10) at admission and 528 (14·6%) of 3621 had moderate-to-severe stroke at randomisation.

Follow-up was completed on July 10, 2024. 319 (8·8%) of 3621 participants died before 90-day follow-up, and 68 (1·9%) participants withdrew from trial treatment. Of those who withdrew, 29 accepted further follow-up or data collection via their general practitioner or medical notes. Three participants were lost to follow-up. 1471 (95·6%) of 1538 participants in the early initiation group and 1401 (94·5%) of 1483 in the delayed initiation group were reported to still be taking the assigned anticoagulation treatment at 90 days.

Primary and secondary outcomes are shown in table 2. The upper limit of the 95% CI for the primary outcome (ie, recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days) was 1·2 percentage points ($p_{non\text{-}inferiority}$=0·0003), which is less than 2 percentage points, our prespecified margin for non-inferiority. We did not identify superiority during our analysis ($p_{superiority}$=0·96). The time-to-event curves for the primary outcome according to allocated treatment are shown in figure 2.

The proportion of participants with symptomatic intracranial haemorrhage within 90 days was 23 (0·6%) of 3621 participants (table 2). The proportions of participants with recurrent ischaemic stroke, systemic embolism, unclassifiable stroke, and all-cause mortality were similar across treatment groups (table 2). Time-to-event plots for all-cause mortality, a composite of the primary outcome or all-cause mortality, a composite of systemic embolism or ischaemic stroke, symptomatic intracranial haemorrhage, recurrent ischaemic stroke, and systemic embolism are shown in the appendix (pp 11–16). There were no significant differences between the treatment groups for secondary outcomes at 90 days, including mortality, a composite of the primary outcome or mortality, major extracranial bleeding, non-major extracranial bleeding, or all major bleeding (table 2).

There was no heterogeneity in any of the primary or secondary outcomes among any prespecified subgroup, including clinical stroke severity, age, sex, reperfusion therapy, or anticoagulation before the qualifying ischaemic stroke (figure 3). Primary and secondary outcomes in the subgroup of patients with severe stroke (ie, with an NIHSS score of >21 points at randomisation, n=68) are shown in the appendix (p 10).

No unexpected serious adverse events were reported.

	Early initiation (n=1814)	Delayed initiation (n=1807)	Adjusted risk difference (95% CI)	p value
Primary outcome*	59 (3·3%)	59 (3·3%)	0·000 (–0·011 to 0·012)	0·96
Recurrent ischaemic stroke	44 (2·4%)	42 (2·3%)	–0·001 (–0·011 to 0·009)	0·84
Symptomatic intracranial haemorrhage	11 (0·6%)	12 (0·7%)	0·001 (–0·004 to 0·006)	0·78
Systemic embolism	2 (0·1%)	4 (0·2%)	0·001 (–0·002 to 0·004)	0·40
Unclassifiable stroke	3 (0·2%)	2 (0·1%)	–0·001 (–0·003 to 0·002)	0·66
All-cause mortality	159 (8·8%)	160 (8·9%)	0·002 (–0·015 to 0·019)	0·83
Primary outcome and mortality	196 (10·8%)	190 (10·5%)	–0·001 (–0·021 to 0·018)	0·88
Major extracranial bleeding	7 (0·4%)	13 (0·7%)	0·004 (–0·001 to 0·009)	0·16
Non-major extracranial bleeding	45 (2·5%)	37 (2·0%)	–0·004 (–0·014 to 0·006)	0·42
All major bleeding (extracranial and intracranial)	18 (1·0%)	25 (1·4%)	0·004 (–0·003 to 0·011)	0·24
Venous thromboembolism	7 (0·4%)	10 (0·6%)	0·002 (–0·003 to 0·006)	0·46

Data are n (%) unless otherwise specified. Risk difference estimates and p values are adjusted for stroke severity (assessed with National Institutes of Health Stroke Scale score) at randomisation. *Composite of recurrent ischaemic stroke, unclassifiable stroke, symptomatic intracranial haemorrhage, and systemic embolism at 90 days.

Table 2: **First occurrence of outcome events during follow-up in the modified intention-to-treat population**

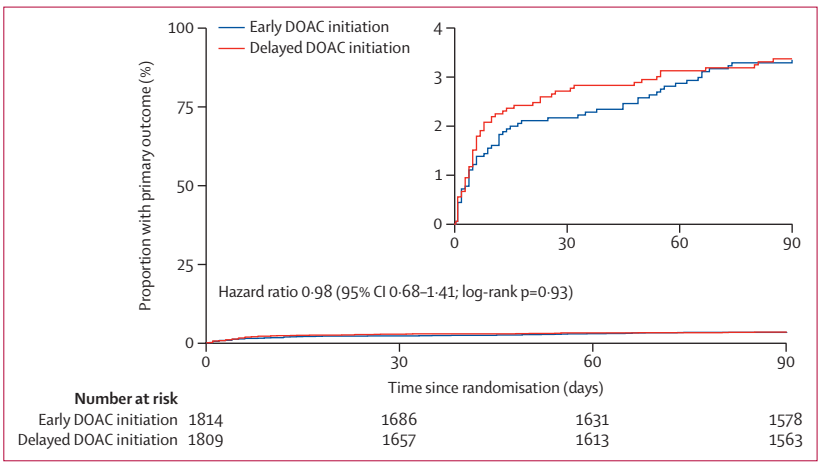

Figure 2: **Time-to-event curves of the primary composite outcome of recurrent ischaemic stroke, symptomatic intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days**
Hazard ratio adjusted for stroke severity (National Institutes of Health Stroke Scale score) at randomisation. DOAC=direct oral anticoagulant.

Discussion

In this trial of 3621 participants with acute ischaemic stroke and atrial fibrillation, the proportions of participants with the composite outcome of recurrent ischaemic stroke, intracranial haemorrhage,

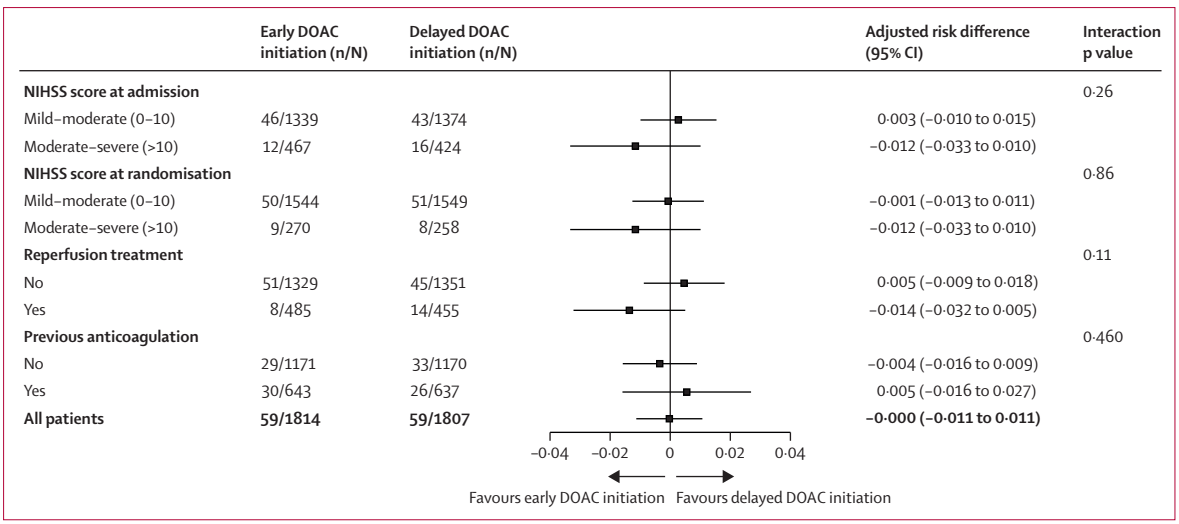

Figure 3: **Forest plot for the primary outcome according to clinically relevant subgroups**
Risk difference was adjusted for stroke severity (based on National Institutes of Health Stroke Scale score at randomisation). p values refer to interaction terms between subgroup characteristics and the DOAC timing with respect to the primary outcome. DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale.

unclassifiable stroke, or systemic embolism were similar in those allocated to receive early (ie, ≤4 days) or delayed (ie, 7–14 days) oral anticoagulation. Early DOAC initiation was non-inferior to delayed DOAC initiation in relation to our prespecified non-inferiority margin of 2 percentage points. The proportion of participants with symptomatic intracranial haemorrhage within 90 days was very low (23 [0·6%] of 3621 participants), and was not influenced by the timing of anticoagulation, indicating that starting a DOAC early after acute ischaemic stroke associated with atrial fibrillation in patients without known contraindications is safe (with regard to symptomatic intracranial haemorrhage). We found no evidence of heterogeneity of the effects of early DOAC initiation according to clinical stroke severity (NIHSS score 0–10 *vs* NIHSS score >10). Our findings are consistent with other trials of early DOAC initiation, including the TIMING,[10] ELAN,[12] and START trials,[25] and taken together with the results of these trials, provide reassurance for the safety of early anticoagulation with a DOAC and do not support the common current guideline-supported practice of delaying oral anticoagulation after acute ischaemic stroke with atrial fibrillation for up to 14 days after moderate-to-severe acute stroke. Early DOAC initiation also has the potential practical advantage of improving the proportion of patients who start secondary prevention treatment before hospital discharge, although this is not shown by our data and should be investigated in further studies.

We note that mortality is a potential competing risk for our primary composite outcome. When we combined mortality with the primary outcome at 90 days, the upper end of the 95% CI was 1·8 percentage points, which is still below the non-inferiority margin of 2·0 percentage points, but slightly closer to the upper margin than in the primary analysis due to the higher event rate and nature of the binomial distribution. Nevertheless, these observations indicate that our findings are robust to the effects of the competing risk of death.

OPTIMAS provides data on a broad population likely to be representative of those with acute stroke and atrial fibrillation, including those with severe stroke. The median NIHSS score on admission in OPTIMAS was 5 (IQR 3–10), which is higher than that observed for all strokes in the most recent UK national stroke audit data (4, 2–10; James M, unpublished) and in a large, multicentre, observational study of patients with ischaemic stroke associated with atrial fibrillation treated with DOACs (4, 2–10).[26] In our study, the proportion of participants with moderate-to-severe stroke (ie, NIHSS score >10) at hospital admission was 891 (24·6%) and at randomisation was 528 (14·6%). We identified no evidence of heterogeneity of the effect of anticoagulation timing in prespecified subgroups, including patients with moderate-to-severe stroke, those treated with reperfusion therapies (ie, intravenous thrombolysis, mechanical thrombectomy, or both), or those taking anticoagulants before their acute ischaemic stroke. Our study included more patients taking an anticoagulant at the time of their stroke than in previous trials (1166 [32·2%] of 3621 participants were taking a DOAC and 114 [3·1%] were taking a vitamin K antagonist), providing important reassurance about the safety of restarting a DOAC within the first 4 days in this patient group. The lack of any interaction of reperfusion treatment with DOAC initiation ($p_{interaction}$=0·11, with a point estimate indicating possible benefit in this subgroup) suggests that DOACs can be safely initiated within 4 days of these interventions. Our findings therefore indicate that early DOAC treatment is safe

(regarding intracranial haemorrhage) across a broad range of patients with acute ischaemic stroke and atrial fibrillation. Our findings do not support delaying restarting anticoagulation beyond the first 4 days (usually with aspirin bridging) in patients who are on treatment with an anticoagulant at the time of their stroke.[27]

Consistent with our findings, the ELAN trial[12] did not identify any heterogeneity of treatment effect related to clinical stroke severity. The median NIHSS score at randomisation in OPTIMAS was 4 (IQR 2–7) compared with a median of 3 (1–6) in the ELAN trial, indicating a population with more severe stroke in OPTIMAS. An advantage of OPTIMAS was that the trial allowed the inclusion of participants with confluent parenchymal haematoma within infarcted brain tissue, for whom there is clinical concern about intracranial bleeding. Although such participants were not eligible according to the ELAN inclusion criteria, a post-hoc ELAN neuroimaging study reported that 56 (2·89%) of 1933 enrolled participants had parenchymal haematoma type 1 or type 2,[13] which did not modify the effect of early DOAC initiation.[28] Future planned brain imaging analyses within OPTIMAS will investigate whether the presence of haemorrhagic transformation of the infarct should still be a consideration when initiating DOAC therapy after ischaemic stroke, along with the effects of other brain imaging biomarkers, including infarct size and the presence of cerebral small vessel disease. We plan to report these findings in a separate publication.

Secular trends in acute stroke care (eg, improvements in acute care and secondary prevention over the first 90 days) might have contributed to a low primary outcome event rate in OPTIMAS and the other trials, ELAN[12] and TIMING.[10] Our tested intervention of early DOAC initiation might be expected to have its greatest effect on ischaemic stroke recurrence within the first 30 days, due to additional protection against early cardiac embolism, in line with the results of the ELAN trial and early dual antiplatelet therapy after ischaemic stroke or transient ischaemic attack.[29] This hypothesis will be investigated in a planned individual participant meta-analysis of the TIMING,[10] ELAN,[12] OPTIMAS, and START[25] trials.[30]

We decided against imaging-based eligibility criteria;[31] although infarct size is a risk factor for haemorrhagic transformation,[32] anticoagulation timing and infarct size have not been shown to interact with respect to the risks of clinically significant haemorrhagic transformation and adverse clinical outcomes, although these considerations often feature in expert guidance.[5] However, large infarct size is considered to be a risk factor for recurrent ischaemic stroke in patients with atrial fibrillation.[33,34] Visual classifications of infarct size are based mainly on vascular anatomy and expert opinion,[32] and accurate measurement requires diffusion-weighted brain MRI (or a delayed CT) and trained raters, increasing the time and complexity of establishing eligibility, an important consideration in a time-sensitive trial. Nevertheless, a substudy of the ELAN trial investigating infarct size measured with a simple classification (ie, mild, moderate, or severe, based on the territory of infarction observed on acute brain imaging with CT or MRI)[35] identified no evidence for an interaction of infarct size with early DOAC treatment.

The larger size of OPTIMAS than previous trials has allowed more precise and reliable estimates of the influence of DOAC timing on recurrent ischaemic stroke or intracranial haemorrhage. Our broad eligibility criteria were intended to give a representative study sample and provide results that are readily applicable to clinical practice. We masked outcome event assessors to the allocated DOAC initiation group and used prespecified objective definitions for major outcomes and independent external adjudication to reduce misclassification of recurrent ischaemic stroke and intracranial haemorrhage events, reducing bias. Nevertheless, some limitations should be considered. No participants in OPTIMAS were randomly assigned to start anticoagulation between 4 days and 7 days after onset, as specified in our trial protocol. This separation between treatment groups aimed to minimise crossovers and ensure that the two groups received different timings of DOAC initiation. Moreover, participants allocated to early DOAC initiation could start treatment at any point within the first 4 days, irrespective of stroke severity and at the discretion of the treating physician, which does not allow us to observe the optimal timing of DOAC initiation during this early period. Nevertheless, our findings do not indicate a need to modify the timing of DOAC initiation based on stroke severity, as suggested in the previously recommended 1-3-6-12 rule. The CATALYST individual participant data meta-analysis[30] will give full coverage of the associations of DOAC timing with clinically important outcomes during the first 2 weeks after stroke onset, with statistical power to explore the optimal timing of DOAC initiation throughout this period in more detail. Although OPTIMAS did not limit inclusion based on clinical stroke severity or infarct size, we included only a few people with very severe strokes and excluded those with the most severe form of haemorrhagic transformation (ie, parenchymal haematoma type 2), limiting our ability to provide definitive guidance in this rare subgroup of patients who are typically considered at greatest risk of intracranial haemorrhage with early DOAC initiation. Regarding the safety outcome of symptomatic intracranial haemorrhage, only 23 events were observed, limiting the statistical power. Finally, although we identified no difference in the composite primary outcome according to DOAC timing, the 95% CI includes a maximum adjusted risk difference of 1·2 percentage points. The CATALYST collaborative individual participant data meta-analysis will provide more precise estimates of the effect of DOAC timing on intracranial haemorrhage and recurrent ischaemic stroke than presented here.

In conclusion, OPTIMAS has shown that early DOAC initiation after ischaemic stroke associated with atrial

fibrillation is non-inferior to delayed initiation for the composite outcome of ischaemic stroke, intracranial haemorrhage, unclassifiable stroke, or systemic embolism at 90 days. There was no increase in the risk of intracranial haemorrhage or reduction in the risk of recurrent ischaemic stroke. Our findings do not support delaying initiation of a DOAC because of concerns about the risk of early intracranial haemorrhage, particularly in people with moderate-to-severe stroke, as guidelines recommend.[9]

Contributors

DJW conceived the idea for the study. DJW, JGB, HC, CJD, STE, MJ, GYHL, BN, NS, and NF contributed to study design and protocol development and to acquisition of funding. H-MD and NA did the statistical analysis, with input from NF. DJW wrote the first draft of the Article. All authors contributed to the collection of data and to the writing of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. H-MD, NA, and NF have accessed and verified the data.

Declaration of interests

DJW reports consulting fees from Novo Nordisk, National Institute for Health and Clinical Excellence, and Alnylam; payments or speaker honoraria from Novo Nordisk, Bayer, and AstraZeneca/Alexion; participation on a data safety monitoring board for the OXHARP trial, participation as Steering Committee Chair for the MACE-ICH and PLINTH trials; serving as President of the British and Irish Association of Stroke Physicians; and holding a National Institute for Health and Care Research Senior Investigator Award. BN reports payments for work in a data safety monitoring board in the HOVID trial and fees from Simbec Orion. MJ reports travel or speaker honoraria from Daiichi-Sankyo, Portola, and Boehringer Ingelheim. HC reports speaker honoraria from Technoclone (paid to UCL Hospitals Charity) and GSK; consulting fees from UCB Biopharma (paid to UCL Hospitals Charity); and advisory board fees from Roche and Argenx. GYHL reports being a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Anthos (no fees received personally), and is a National Institute for Health and Care Research Senior Investigator. RH reports grants from the National Institute for Health and Care Research for the Dementia Policy Research Unit—Queen Mary and the Research Support Service and being Co-chair of the EU Transforming Health and Care Systems funding board in 2023. GAF reports receiving consulting fees from AstraZeneca for a project on management of stroke due to intracerebral haemorrhage (payment to his employer) and Bayer (for lecture on models of the National Health Service industry working) and is Chief Executive of Health Innovation (Oxford and Thames Valley), which has multiple joint working agreements and medical education grants with industry partners that have contracts with Oxford University Hospitals NHS Trust. NF reports consulting fees received from ALK, Sanofi Aventis, Gedeon Richter, Abbot, Galderma, AstraZeneca, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune, and Gilead. All other authors declare no competing interests.

Data sharing

A fully anonymised version of the dataset used for analysis with individual participant data and a data dictionary can be made available for other researchers following application to the corresponding author. A data sharing agreement must be put in place before any data are shared. Written proposals will be assessed by members of the OPTIMAS trial steering committee and a decision made about the appropriateness of the use of data.

Acknowledgments

The trial was sponsored by UCL. We sincerely thank all participants, their relatives or carers, their hospital doctors, and their primary care practitioners; the trial steering committee; the independent data monitoring committee; and the independent external event adjudication committee. We acknowledge support from the National Institute for Health Research and Care Clinical Research Network (stroke) and thank all research staff at participating sites for their valued work on successfully delivering the trial. We thank the British Heart Foundation for generously funding OPTIMAS with a Clinical Study Project grant (CS/17/6/33361), including continuing to support the trial during the recruitment challenges associated with the COVID-19 pandemic.

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